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Case Docket No. 12564-9021
Date August 25, 1999

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ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir:

Transmitted herewith for filing under 37 C.F.R. §1.53(b) is the patent application of:
Inventor(s): Gertrud HÖTTEN, Helge NEIDHARDT, Rolf BECHTOLD and Jen POHL

For: **GROWTH/DIFFERENTIATION FACTORS OF THE TGF-β FAMILY**
This application is a divisional of Application No. 08/289,222

XX Return Receipt Postcard
XX Specification (34 pages)
XX -3- sheets of drawings
XX A copy of Sequence Listing and Statement with disk
XX A Preliminary Amendment
XX Declaration and Power of Attorney
XX Copy from a prior application
XX The disclosure of the prior application, from which a copy of the declaration is supplied as noted above is considered as being a part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
XX Assignment was filed in parent Appln. No. 08/289,222, Reel/Frame 7426/0515.
XX Priority of German application, Serial No. P44 23 190.3 filed 01/07/1994 and European application, Serial No. 92 102 324.8 filed 12/02/1992 is claimed under 35 U.S.C. §119.
XX An Information Disclosure Statement with PTO-1449
XX A filing fee, calculated as shown below, including claims added or deleted in the Preliminary Amendment (**Check No. 20576**):

	(Col. 1)	(Col. 2)	Small Entity			Other Than A Small Entity	
FOR:	No. Filed	No. Extra	RATE	FEE		RATE	FEE
BASIC FEE				$380	or		$760
TOTAL CLAIMS	12 - 20 =	-0-	× 9 =		or	× 18 =	
INDEP CLAIMS	6 - 3 =	3	× 39 =		or	× 78 =	$234
_ MULTIPLE DEPENDENT CLAIM PRESENTED			+130 =		or	+260 =	
			TOTAL		or		$994

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

HOTTEN et al.

Serial Number: Unknown

Group Art Unit: Unknown

Filed: August 25, 1999

Examiner: Unknown

For: GROWTH/DIFFERENTIATION FACTORS OF THE TGF-β FAMILY

STATEMENT UNDER 37 CFR §1.821(C)

Assistant Commissioner
of Patents and Trademarks
Washington, D.C. 20231

August 25, 1999

Sir:

In accordance with 37 C.F.R.1.821(C), applicants are submitting herewith the Sequence Listing for the above-identified application both in paper copy form and in computer readable form.

The name of the file on the computer readable form is 5649021.APP. The paper copy and the computer readable form are the same.

In the event that this paper is not considered to be timely filed, applicants hereby petition for an appropriate extension of time. The fee for any such extension may be charged to our Deposit Account No. 14-1060, along with any other fees with respect to this paper.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

HÖTTEN et al.

Serial No.: unknown

Filed: August 20, 1999

For: GROWTH/DIFFERENTIATION FACTORS OF THE TGF-β FAMILY

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

August 25, 1999

Sir:

Prior to calculation of the filing fee and prior to the examination of this application, please amend the above-identified application as follows:

IN THE CLAIMS:

Kindly cancel claims 1-19 without prejudice or disclaimer.

Please add the following new claims to the application.

--20. An antibody or antibody fragment which specifically binds to a protein of the TGF-ß family wherein said protein is encoded by a DNA comprising a nucleotide sequence selected from the following group:

(a) the nucleotide sequence as shown in SEQ ID NO:1,

(b) a nucleotide sequence which is degenerate as a result of the genetic code to the nucleotide sequence of (a), and

(c) fragments of (a) or (b) which encode a protein which has essentially the same

cartilage or bone inducing activities as a mature protein encoded by the nucleotide sequence of SEQ ID NO:1.

21. The antibody according to claim 20, wherein said antibody is a monoclonal antibody.

22. An antibody or antibody fragment according to claim 20, which specifically binds to a protein of the TGF-ß family wherein said protein comprises the amino acid sequence according to SEQ ID NO:3.

23. The antibody according to claim 22, wherein said antibody is a monoclonal antibody.

24. An antibody or antibody fragment which specifically binds a protein of the TGF-ß family, wherein said protein is encoded by a DNA comprising a nucleotide sequence selected from the following group:

(a) the nucleotide sequence as shown in SEQ ID NO:2,

(b) a nucleotide sequence which is degenerate as a result of the genetic code to the DNA of (a),

(c) a nucleotide sequence which hybridizes under the following stringent hybridization conditions to the DNA in (a), or (b): hybridization at a salt concentration of 4X SSC at 62°-66°C followed by a one-hour wash with 0.1X SSC and 0.1% SDS at 62°-66°C, and

(d) fragments of (a), (b) or (c) which encode a protein which has essentially the same cartilage or bone inducing activity as a mature protein encoded by the nucleotide sequence of SEQ ID NO:2.

25. An antibody or antibody fragment according to claim 24, wherein said protein comprises the amino acid sequence according to SEQ ID NO:4.

26. The antibody according to claim 25, wherein said antibody is a monoclonal antibody.

27.The antibody according to claim 24, wherein said antibody is a monoclonal antibody.

28. A method for detecting a protein of the TGF-ß family,

comprising incubating an antibody or antibody fragment which specifically binds to a protein of the TGF-ß family with a sample suspected of containing said protein, and

detecting any antibody/protein complex formed as an indication of the presence of said protein,

wherein said protein is encoded by a DNA comprising a nucleotide sequence selected from the following group:

(a) the nucleotide sequence as shown in SEQ ID NO:1,

(b) a nucleotide sequence which is degenerate as a result of the genetic code to the nucleotide sequence of (a), and

(c) fragments of (a) or (b) which encode a protein which has essentially the same cartilage or bone inducing activities as a mature protein encoded by the nucleotide sequence of SEQ ID NO:1.

29. A method for detecting a protein of the TGF-ß family, comprising

incubating an antibody or antibody fragment which specifically binds to said protein of the TGF-ß family with a sample suspected of containing said protein, and

detecting any antibody/protein complex formed as an indication of the presence of said protein,

wherein said protein is encoded by a DNA comprising a nucleotide sequence selected from the following group:

(a) the nucleotide sequence as shown in SEQ ID NO:2,

(b) a nucleotide sequence which is degenerate as a result of the genetic code to the DNA of (a),

(c) a nucleotide sequence which hybridizes under the following stringent hybridization conditions to the DNA in (a), or (b): hybridization at a salt concentration of 4X SSC at 62°-66°C followed by a one-hour wash with 0.1X SSC and 0.1% SDS at 62°-66°C, and

(d) fragments of (a), (b) or (c) which encode a protein which has essentially the same cartilage or bone inducing activity as a mature protein encoded by the nucleotide sequence of SEQ ID NO:2.

30. A kit for detecting a protein of the TGF-ß family, comprising

an antibody or antibody fragment which specifically binds to a protein of the TGF-ß family, and

a reaction buffer,

wherein said protein is encoded by a DNA comprising a nucleotide sequence selected from the following group:

(a) the nucleotide sequence as shown in SEQ ID NO:1,

(b) a nucleotide sequence which is degenerate as a result of the genetic code to the nucleotide sequence of (a), and

(c) fragments of (a) or (b) which encode a protein which has essentially the same cartilage or bone inducing activities as a mature protein encoded by the nucleotide sequence of SEQ ID NO:1.

31. A kit for detecting a protein of the TGF-ß family, comprising

an antibody or antibody fragment which specifically binds to a protein of the TGF-ß family, and

a reaction buffer,

wherein said protein is encoded by a DNA comprising a nucleotide sequence selected from the following group:

(a) the nucleotide sequence as shown in SEQ ID NO:2,

(b) a nucleotide sequence which is degenerate as a result of the genetic code to the DNA of (a),

(c) a nucleotide sequence which hybridizes under the following stringent hybridization conditions to the DNA in (a), or (b): hybridization at a salt concentration of

4X SSC at 62°-66°C followed by a one-hour wash with 0.1X SSC and 0.1% SDS at 62°-66°C, and

(d) fragments of (a), (b) or (c) which encode a protein which has essentially the same cartilage or bone inducing activity as a mature protein encoded by the nucleotide sequence of SEQ ID NO:2. --

REMARKS

The above amendments have been made to put the application into better condition for examination.

In the event that any fees are due in connection with this paper, please charge our Deposit Account No. 14-1060.

Respectfully submitted,

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DNA Sequences Encoding Novel Growth/ Differentiation Factors

The present invention relates to DNA sequences encoding novel growth/differentiation factors of the TGF-ß family. In particular, it relates to novel DNA sequences encoding TGF-ß-like proteins, to the isolation of said DNA sequences, to expression plasmids containing said DNA, to microorganisms transformed by said expression plasmid, to the production of said protein by culturing said transformant, and to pharmaceutical compositions containing said protein. The TGF-ß family of growth factors comprising BMP, TGF, and Inhibin related proteins (Roberts and Sporn, Handbook of Experimental Pharmacology 95 (1990), 419-472) is of particular relevance in a wide range of medical treatments and applications. These factors are useful in processes relating to wound healing and tissue repair. Furthermore, several members of the TGF-ß family are tissue inductive, especially osteo-inductive, and consequently play a crucial role in inducing cartilage and bone development.

Wozney, Progress in Growth Factor Research 1 (1989), 267-280 and Vale et al., Handbook of Experimental Pharmacology 95 (1990), 211-248 describe different growth factors such as those relating to the BMP (bone morphogenetic proteins) and the Inhibin group. The members of these groups share significant structural similarity. The precursor of the protein is composed of an aminoterminal signal sequence, a propeptide and a carboxyterminal sequence of about 110 amino acids, which is subsequently cleaved from the precursor and represents the mature protein. Furthermore, their members are defined by virtue of amino acid sequence homology. The

mature protein contains the most conserved sequences, especially seven cysteine residues which are conserved among the family members. The TGF-ß-like proteins are multifunctional, hormonally active growth factors. They also share related biological activities such as chemotactic attraction of cells, promoting cell differentiation and their tissue-inducing capacity, such as cartilage- and bone-inducing capacity. U.S. Patent No. 5,013,649 discloses DNA sequences encoding osteo-inductive proteins termed BMP-2 proteins (bone morphogenetic protein), and U.S. patent applications serial nos. 179 101 and 179 197 disclose the BMP proteins BMP-1 and BMP-3. Furthermore, many cell types are able to synthesize TGF-ß-like proteins and virtually all cells possess TGF-ß receptors.

Taken together, these proteins show differences in their structure, leading to considerable variation in their detailed biological function. Furthermore, they are found in a wide variety of different tissues and developmental stages. Consequently, they might possess differences concerning their function in detail, for instance the required cellular physiological environment, their lifespan, their targets, their requirement for accessory factors, and their resistance to degradation. Thus, although numerous proteins exhibiting tissue-inductive, especially osteo-inductive potential are described, their natural role in the organism and, more importantly, their medical relevance must still be elucidated in detail. The occurrence of still-unknown members of the TGF-ß family relevant for osteogenesis or differentiation/induction of other tissues is strongly suspected. However, a major problem in the isolation of these new TGF-ß-like proteins is that their functions cannot yet be described precisely enough for the design of a discriminative bioassay. On the other hand, the expected nucleotide sequence homology to known members of the family would be too low to

allow for screening by classical nucleic acid hybridization techniques. Nevertheless, the further isolation and characterization of new TGF-ß-like proteins is urgently needed in order to get hold of the whole set of induction and differentiation proteins meeting all desired medical requirements. These factors might find useful medical applications in defect healing and treatments of degenerative disorders of bone and/or other tissues like, for example, kidney and liver.

Thus, the technical problem underlying the present invention essentially is to provide DNA sequences coding for new members of the TGF-ß protein family having mitogenic and/or differentiation-inductive, e.g. osteo-inductive potential.

The solution to the above technical problem is achieved by providing the embodiments characterized in claims 1 to 17. Other features and advantages of the invention will be apparent from the description of the preferred embodiments and the drawings. The sequence listings and drawings will now briefly be described.

SEQ ID NO. 1 shows the nucleotide sequence of MP-52, i.e. the embryo derived sequence corresponding to the mature peptide and most of the sequence coding for the propeptide of MP-52.

Some of the propeptide sequence at the 5'-end of MP-52 has not been characterized so far.

SEQ ID NO. 2 shows the nucleotide sequence of MP-121, i.e. the liver derived sequence corresponding to the mature peptide, the sequence coding for the propeptide of MP-121, and sequences 5' and 3' to the coding region.

The start codon begins with nucleotide 128 of SEQ ID NO.2. The sequence coding for the mature MP121 polypeptide begins with nucleotide 836 of SEQ ID NO. 2. The stop codon begins with nucleotide 1184 of SEQ ID NO. 2. The sequence coding for the precursor protein has a length of 1056 bp. The sequence coding for the propeptide has a length of 708 bp and the sequence coding for the mature peptide has a length of 348 bp.

SEQ ID NO. 3 shows the amino acid sequence of MP-52 as deduced from SEQ ID NO. 1.

SEQ ID NO. 4 shows the amino acid sequence of MP-121 as deduced from sequence SEQ ID NO.2. The sequence of the mature polypeptide begins with amino acid 237 of SEQ ID NO. 4. The precursor protein has a length of 352 amino acids. The propeptide and the mature peptide have a length of 236 and 116 amino acids, respectively.

SEQ ID NO. 5 shows a part of the nucleotide sequence of the liver derived sequence of MP-121.

SEQ ID NO. 6 shows a part of the nucleotide sequence of the embryo derived sequence of MP-52.

The shorter DNA-sequences SEQ ID NO. 5 and 6 can be useful for example for isolation of further members of the TGF-ß-protein family.

Figure 1 shows an alignment of the amino acid sequences of MP-52 and MP-121 starting from the first of the seven conserved cysteines with some related proteins. 1a shows the alignment of MP-52 with some members of the BMP protein family; 1b shows the alignment of MP-121 with some members of the Inhibin protein family. * indicates that the amino acid

is the same in all proteins compared; + indicates that the amino acid is the same in at least one of the proteins compared with MP-52 (Fig. 1a) or MP-121 (Fig. 1b).

Figure 2 shows the nucleotide sequences of the oligo-nucleotide primer as used in the present invention and an alignment of these sequences with known members of the TGF-ß family. M means A or C; S means C or G; R means A or G; and K means G or T. 2a depicts the sequence of the primer OD; 2b shows the sequence of the primer OID.

The present invention relates to novel TGF-ß-like proteins and provides DNA sequences contained in the corresponding genes. Such sequences include nucleotide sequences comprising the sequence

ATGAACTCCATGGACCCCGAGTCCACA and

CTTCTCAAGGCCAACACAGCTGCAGGCACC

and in particular sequences as illustrated in SEQ ID Nos. 1 and 2, allelic derivatives of said sequences and DNA sequences degenerated as a result of the genetic code for said sequences. They also include DNA sequences hybridizing under stringent conditions with the DNA sequences mentioned above and containing the following amino acid sequences:

Met-Asn-Ser-Met-Asp-Pro-Glu-Ser-Thr or

Leu-Leu-Lys-Ala-Asn-Thr-Ala-Ala-Gly-Thr.

Although said allelic, degenerate and hybridizing sequences may have structural divergencies due to naturally occurring mutations, such as small deletions or substitutions, they will usually still exhibit essentially the same useful properties, allowing their use in basically the same medical applications.

According to the present invention, the term "hybridization" means conventional hybridization conditions, preferably

conditions with a salt concentration of 6 x SSC at 62° to 66°C followed by a one-hour wash with 0.6 x SSC, 0.1% SDS at 62° to 66°C. The term "hybridization" preferably refers to stringent hybridization conditions with a salt concentration of 4 x SSC at 62°-66°C followed by a one-hour wash with 0.1 x SSC, 0.1% SDS at 62°-66°C.

Important biological activities of the encoded proteins, preferably MP-52, comprise a mitogenic and osteo-inductive potential and can be determined in assays according to Seyedin et al., PNAS 82 (1985), 2267-2271 or Sampath and Reddi, PNAS 78 (1981), 7599-7603.

The biological properties of the proteins according to the invention, preferably MP-121, may be determined, e.g., by means of the assays according to Wrana et al. (Cell 71, 1003-1014 (1992)), Ling et al. (Proc. Natl. Acad. of Science, 82, 7217-7221 (1985)), Takuwa et al. (Am. J. Physiol., 257, E797-E803 (1989)), Fann and Patterson (Proc. Natl. Acad. of Science, 91, 43-47 (1994)), Broxmeyer et al. (Proc. Natl. Acad. of Science, 85, 9052-9056 (1988)), Green et al. (Cell, 71, 731-739 (1992)), Partridge et al. (Endocrinology, 108, 213-219 (1981)) or Roberts et al. (PNAS 78, 5339-5343 (1981)).

Preferred embodiments of the present invention are DNA sequences as defined above and obtainable from vertebrates, preferably mammals such as pig or cow and from rodents such as rat or mouse, and in particular from primates such as humans.

Particularly preferred embodiments of the present invention are the DNA sequences termed MP-52 and MP-121 which are shown in SEQ ID Nos. 1 and 2. The corresponding transcripts of MP-52 were obtained from embryogenic tissue and code for a

protein showing considerable amino acid homology to the mature part of the BMP-like proteins (see Fig. 1a). The protein sequences of BMP2 (=BMP2A) and BMP4 (=BMP2B) are described in Wozney et al., Science Vol 242, 1528-1534 (1988). The respective sequences of BMP5, BMP6 and BMP7 are described in Celeste et al., Proc.Natl.Acad.Sci. USA Vol 87, 9843-9847 (1990). Some typical sequence homologies, which are specific to known BMP-sequences only, were also found in the propeptide part of MP-52, whereas other parts of the precursor part of MP-52 show marked differences to BMP-precursors. The mRNA of MP-121 was detected in liver tissue, and its correspondig amino acid sequence shows homology to the amino acid sequences of the Inhibin protein chains (see Fig. 1b). cDNA sequences encoding TGF-ß-like proteins have not yet been isolated from liver tissue, probably due to a low abundance of TGF-ß specific transcripts in this tissue. In embryogenic tissue, however, sequences encoding known TGF-ß-like proteins can be found in relative abundance. The inventors have recently detected the presence of a collection of TGF-ß-like proteins in liver as well. The high background level of clones related to known factors of this group presents the main difficulty in establishing novel TGF-ß-related sequences from these and probably other tissues. In the present invention, the cloning was carried out according to the method described below. Once the DNA sequence has been cloned, the preparation of host cells capable of producing the TGF-ß-like proteins and the production of said proteins can be easily accomplished using known recombinant DNA techniques comprising constructing the expression plasmids encoding said protein and transforming a host cell with said expression plasmid, cultivating the transformant in a suitable culture medium, and recovering the product having TGF-ß-like activity.

Thus, the invention also relates to recombinant molecules comprising DNA sequences as described above, optionally linked to an expression control sequence. Such vectors may be useful in the production of TGF-ß-like proteins in stably or transiently transformed cells. Several animal, plant, fungal and bacterial systems may be employed for the transformation and subsequent cultivation process. Preferably, expression vectors which can be used in the invention contain sequences necessary for the replication in the host cell and are autonomously replicable. It is also preferable to use vectors containing selectable marker genes which can be easily selected for transformed cells. The necessary operation is well-known to those skilled in the art.

It is another object of the invention to provide a host cell transformed by an expression plasmid of the invention and capable of producing a protein of the TGF-ß family. Examples of suitable host cells include various eukaryotic and prokaryotic cells, such as E. coli, insect cells, plant cells, mammalian cells, and fungi such as yeast.

Another object of the present invention is to provide a protein of the TGF-ß family encoded by the DNA sequences described above and displaying biological features such as tissue-inductive, in particular osteo-inductive and/or mitogenic capacities possibly relevant to therapeutical treatments. The above-mentioned features of the protein might vary depending upon the formation of homodimers or heterodimers. Such structures may prove useful in clinical applications as well. The amino acid sequence of the especially preferred proteins of the TGF-ß-family (MP-52 and MP-121) are shown in SEQ ID NO. 3 and SEQ ID NO. 4.

It is a further aspect of the invention to provide a process for the production of TGF-ß-like proteins. Such a process

comprises cultivating a host cell being transformed with a DNA sequence of the present invention in a suitable culture medium and purifying the TGF-ß-like protein produced. Thus, this process will allow the production of a sufficient amount of the desired protein for use in medical treatments or in applications using cell culture techniques requiring growth factors for their performance. The host cell is obtainable from bacteria such as Bacillus or Escherichia coli, from fungi such as yeast, from plants such as tobacco, potato, or Arabidopsis, and from animals, in particular vertebrate cell lines such as the Mo-, COS- or CHO cell line.

Yet another aspect of the present invention is to provide a particularly sensitive process for the isolation of DNA sequences corresponding to low abundance mRNAs in the tissues of interest. The process of the invention comprises the combination of four different steps. First, the mRNA has to be isolated and used in an amplification reaction using olignucleotide primers. The sequence of the oligonucleotide primers contains degenerated DNA sequences derived from the amino acid sequence of proteins related to the gene of interest. This step may lead to the amplification of already known members of the gene family of interest, and these undesired sequences would therefore have to be eliminated. This object is achieved by using restriction endonucleases which are known to digest the already-analyzed members of the gene family. After treatment of the amplified DNA population with said restriction endonucleases, the remaining desired DNA sequences are isolated by gel electrophoresis and reamplified in a third step by an amplification reaction, and in a fourth step they are cloned into suitable vectors for sequencing. To increase the sensitivity and efficiency, steps two and three are repeatedly performed, at least two times in one embodiment of this process.

In a preferred embodiment, the isolation process described above is used for the isolation of DNA sequences from liver tissue. In a particularly preferred embodiment of the above-described process, one primer used for the PCR experiment is homologous to the polyA tail of the mRNA, whereas the second primer contains a gene-specific sequence. The techniques employed in carrying out the different steps of this process (such as amplification reactions or sequencing techniques) are known to the person skilled in the art and described, for instance, in Sambrook et al., 1989, "Molecular Cloning: A laboratory manual", Cold Spring Harbor Laboratory Press.

It is another object of the present invention to provide pharmaceutical compositions containing a therapeutically-effective amount of a protein of the TGF-ß family of the present invention. Optionally, such a composition comprises a pharmaceutically acceptable carrier. Such a therapeutic composition can be used in wound healing and tissue repair as well as in the healing of bone, cartilage, or tooth defects, either individually or in conjunction with suitable carriers, and possibly with other related proteins or growth factors. Thus, a therapeutic composition of the invention may include, but is not limited to, the MP-52 encoded protein in conjunction with the MP-121 encoded protein, and optionally with other known biologically-active substances such as EGF (epidermal growth factor) or PDGF (platelet derived growth factor). Another possible clinical application of a TGF-ß-like protein is the use as a suppressor of the immuno response, which would prevent rejection of organ transplants. The pharmaceutical composition comprising the proteins of the invention can also be used prophylactically, or can be employed in cosmetic plastic surgery. Furthermore, the application of the composition is not limited to humans but can include animals, in particular domestic animals, as well. Possible applications of the pharmaceutical composition

according to the invention include furthermore treatment or prevention of connective tissue, skin, mucous membrane, endothelial, epithelial, neuronal or renal defects, use in the case of dental implants, use as a morphogenic factor used for inducing liver tissue growth, induction of the proliferation of precursor cells or bone marrow cells, for maintaining a differentiated state and the treatment of impaired fertility or for contraception.

Finally, another object of the present invention is an antibody or antibody fragment, which is capable of specifically binding to the proteins of the present invention. Methods to raise such specific antibody are general knowledge. Preferably such an antibody is a monoclonal antibody. Such antibodies or antibody fragments might be useful for diagnostic methods.

The following examples illustrate in detail the invention disclosed, but should not be construed as limiting the invention.

Example 1
Isolation of MP-121

1.1 Total RNA was isolated from human liver tissue (40-year-old-male) by the method of Chirgwin et al., Biochemistry 18 (1979), 5294-5299. Poly A^+ RNA was separated from total RNA by oligo (dT) chromatography according to the instructions of the manufacturer (Stratagene Poly (A) Quick columns).

1.2 For the reverse transcription reaction, poly A^+ RNA (1-2.5 μg) derived from liver tissue was heated for 5 minutes to 65°C and cooled rapidly on ice. The reverse transcription reagents containing 27 U RNA guard

(Pharmacia), 2.5 µg oligo $d(T)_{12-18}$ (Pharmacia) 5 x buffer (250 mM Tris/HCl pH 8.5; 50 mM $MgCl_2$; 50 mM DTT; 5 mM each dNTP; 600 mM KCl) and 20 units avian myeloblastosis virus reverse transcriptase (AMV, Boehringer Mannheim) per µg poly (A^+) RNA were added. The reaction mixture (25 µl) was incubated for 2 hours at 42°C. The liver cDNA pool was stored at -20°C.

1.3 The deoxynucleotide primers OD and OID (Fig. 2) designed to prime the amplification reaction were generated on an automated DNA-synthesizer (Biosearch). Purification was done by denaturating polyacrylamide gel electrophoresis and isolation of the main band from the gel by isotachophoresis. The oligonucleotides were designed by aligning the nucleic acid sequences of some known members of the TGF-ß family and selecting regions of the highest conservation. An alignment of this region is shown in Fig. 2. In order to facilitate cloning, both oligonucleotides contained EcoR I restriction sites and OD additionally contained an Nco I restriction site at its 5' terminus.

1.4 In the polymerase chain reaction, a liver-derived cDNA pool was used as a template in a 50 µl reaction mixture. The amplification was performed in 1 x PCR-buffer (16.6 mM $(NH_4)_2SO_4$; 67 mM Tris/HCl pH 8.8; 2 mM $MgCl_2$; 6.7 µM EDTA; 10 mM ß-mercaptoethanol; 170 µg/ml BSA (Gibco)), 200 µM each dNTP (Pharmacia), 30 pmol each oligonucleotide (OD and OID) and 1.5 units Taq polymerase (AmpliTaq, Perkin Elmer Cetus). The PCR reaction contained cDNA corresponding to 30 ng of poly (A^+) RNA as staring material. The reaction mixture was overlayed by paraffine and 40 cycles (cycle 1: 80s 93°C/40s 52°C/40s 72°C; cycles 2-9: 60s 93°C/40s 52°C/40s 72°C; cycles 10-29: 60s 93°C/40s 52°C/60s

72°C; cycles 30-31: 60s 93°C/40s 52°C/90s 72°C; cycle 40: 60s 93°C/40s 52°C/420s 72°C) of the PCR were performed. Six PCR-reaction mixtures were pooled, purified by subsequent extractions with equal volumes of phenol, phenol/chloroform (1:1 (v/v)) and chloroform/isoamylalcohol (24:1 (v/v)) and concentrated by ethanol precipitation.

1.5 One half of the obtained PCR pool was sufficient for digestion with the restriction enzymes Sph I (Pharmacia) and AlwN I (Biolabs). The second half was digested in a series of reactions by the restriction enzymes Ava I (BRL), AlwN I (Biolabs) and Tfi I (Biolabs). The restriction endonuclease digestions were performed in 100 µl at 37°C (except Tfi I at 65°C) using 8 units of each enzyme in a 2- to 12-hour reaction in a buffer recommended by the manufacturer.

1.6 Each DNA sample was fractioned by electrophoresis using a 4% agarose gel (3% FMC Nusieve agarose, Biozym and 1% agarose, BRL) in Tris borate buffer (89 mM Trisbase, 89 mM boric acid, 2 mM EDTA, pH 8). After ethidiumbromide staining uncleaved amplification products (about 200 bp; size marker was run in parallel) were excised from the gel and isolated by phenol extraction: an equal volume of phenols was added to the excised agarose, which was minced to small pieces, frozen for 10 minutes, vortexed and centrifuged. The aqueous phase was collected, the interphase reextracted by the same volume TE-buffer, centrifuged and both aqueous phases were combined. DNA was further purified twice by phenol/chloroform and once by chloroform/isoamylalcohol extraction.

1.7 After ethanol precipitation, one fourth or one fifth of the isolated DNA was reamplified using the same

52°C/60s 72°C; cycle 13: 60s 93°C/40s 52°C/420s 72°C). The reamplification products were purified, restricted with the same enzymes as above and the uncleaved products were isolated from agarose gels as mentioned above for the amplification products. The reamplification followed by restriction and gel isolation was repeated once.

1.8 After the last isolation from the gel, the amplification products were digested by 4 units EcoR I (Pharmacia) for 2 hours at 37°C using the buffer recommended by the manufacturer. One fourth of the restriction mixture was ligated to the vector pBluescriptII SK+ (Stratagene) which was digested likewise by EcoR I. After ligation, 24 clones from each enzyme combination were further analyzed by sequence analysis. The sample restricted by AlwN I and Sph I contained no new sequences, only BMP6 and Inhibin ßA sequences. 19 identical new sequences, which were named MP-121, were found by the Ava I, AlwN I and Tfi I restricted samples. The MP-121 containing plasmids were called pSK MP-121 (OD/OID). One sequence differed from this mainly-found sequence by two nucleotide exchanges. Ligation reaction and transformation in E. coli HB101 were performed as described in Sambrook et al., Molecular cloning: A laboratory manual (1989). Transformants were selected by Ampicillin resistance and the plasmid DNAs were isolated according to standard protocols (Sambrook et al. (1989)). Analysis was done by sequencing the double-stranded plasmids by "dideoxyribonucleotide chain termination sequencing" with the sequencing kit "Sequenase Version 2.0" (United States Biochemical Corporation).

The clone was completed to the 3' end of the c-DNA by a method described in detail by Frohman (Amplifications, published by Perkin-Elmer Corporation, issue 5 (1990), pp 11-15). The same liver mRNA which was used for the isolation of the first fragment of MP-121 was reverse transcribed using a primer consisting of oligo dT (16 residues) linked to an adaptor primer ($AGAATTCGCATGCCATGGTCGACGAAGC(T)_{16}$). Amplification was performed using the adaptor primer (AGAATTCGCATGCCATGGTCGACG) and an internal primer (GGCTACGCCATGAACTTCTGCATA) of the MP-121 sequence. The amplification products were reamplified using a nested internal primer (ACATAGCAGGCATGCCTGGTATTG) of the MP-121 sequence and the adaptor primer. The reamplification products were cloned after restriction with Sph I in the likewise restricted vector pT7/T3 U19 (Pharmacia) and sequenced with the sequencing kit "Sequenase Version 2.0" (United States Biochemical Corporation). Clones were characterized by their sequence overlap to the 3' end of the known MP-121 sequence.

One clone, called p121Lt 3' MP13, was used to isolate a NcoI (blunt ended with T4 polymerase)/SphI fragment. This fragment was ligated into a pSK MP-121 (OD/OID) vector, where the OD primer sequence was located close to the T7 primer sequence of the pSK+ multiple cloning site, opened with SphI/SmaI. The resulting plasmid was called pMP121DFus6. It contains MP-121 specific sequence information starting from position 922 and ending with position 1360 of SEQ ID NO. 2.

1.9 Using a DdeI fragment of pMP-121DFus6 as a probe, ranging from nucleotide 931 to nucleotide 1304 of SEQ ID NO. 2, a human liver cDNA library (Clontech, # HL3006b, Lot 36223) was screened by a common method described in

detail by Ausubel et al. (Current Protocols in Molecular Biology, published by Greene Publishing Associates and Wiley-Interscience (1989)). From 8.1 x 10^5 phages, 24 mixed clones were isolated and re-screened using the DdeI fragment. 10 clones were confirmed and the EcoRI fragments subcloned into Bluescript SK (Stratagene, # 212206). EcoRI restriction analysis showed that one clone (SK121 L9.1, deposited by the DSM (#9177) has an insert of about 2.3 kb. This clone contains the complete reading frame of the MP121 gene and further information to the 5' and 3' end in addition to the sequence isolated from mRNA by the described amplification methods. The complete sequence of the EcoRI insert of SK121 L9.1 is shown in SEQ ID NO.2. The reading frame of the MP-121 gene could be confirmed by sequencing of another clone (SK121 L11.1), having the identical reading frame sequence as SK121 L9.1. The beginning of the start codon of the MP-121 sequence of SK121 L9.1 could be determined at position 128 of SEQ ID NO.2, since there are three stop codons in-frame in front of the start codon at positions 62, 77 and 92. The start site of the mature MP-121 is at position 836 of SEQ ID NO.2 in sequence analogy to other members of the TGF-ß-family, corresponding to amino acid 237 in SEQ ID NO.4. The stop codon is at position 1184 of SEQ ID NO.2.

Plasmid SK121 L9.1 was deposited under number 9177 at DSM (Deutsche Sammlung von Mikroorganismen und Zellkulturen), Mascheroder Weg 1b, Braunschweig, on 26.04.94).

Example 2
Isolation of MP-52

A further cDNA sequence, MP-52, was isolated according to the above described method (Example 1) by using RNA from human embryo (8-9 weeks old) tissue. The PCR reaction contained cDNA corresponding to 20 ng of poly (A^+)RNA as starting material. The reamplification step was repeated twice for both enzyme combinations. After ligation, 24 clones from each enzyme combination were further analyzed by sequence analysis. The sample resticted by AlwN I and Sph I yielded a new sequence which was named MP-52. The other clones comprised mainly BMP6 and one BMP7 sequence. The sample restricted by Ava I, AlwN I and Tfi I contained no new sequences, but consisted mainly of BMP7 and a few Inhibin ßA sequences.

The clone was completed to the 3' end according to the above described method (Example 1). The same embryo mRNA, which was used for the isolation of the first fragment of MP-52, was reverse transcribed as in Example 1. Amplification was performed using the adaptor primer (AGAATTCGCATGCCATGGTCGACG) and an internal primer (CTTGAGTACGAGGCTTTCCACTG) of the MP-52 sequence. The amplification products were reamplified using a nested adaptor primer (ATTCGCATGCCATGGTCGACGAAG) and a nested internal primer (GGAGCCCACGAATCATGCAGTCA) of the MP-52 sequence. The reamplification products were cloned after restriction with Nco I in a likewise restricted vector (pUC 19 (Pharmacia #27-4951-01) with an altered multiple cloning site containing a unique Nco I restriction site) and sequenced. Clones were characterized by their sequence overlap to the 3' end of the known MP-52 sequence. Some of these clones contain the last 143 basepairs of the 3' end of the sequence shown in SEQ ID NO: 1 and the 0,56 kb 3' non translated region (sequence not shown). One of these was used

as a probe to screen a human genomic library (Stratagene #946203) by a common method described in detail by Ausubel et al. (Current Protocols in Molecular Biology, published by Greene publishing Associates and Wiley-Interscience (1989)). From $8x10^5$ λ phages one phage (λ 2.7.4) which was proved to contain an insert of about 20 kb, was isolated and deposited by the DSM (#7387). This clone contains in addition to the sequence isolated from mRNA by the described amplification methods sequence information further to the 5' end. For sequence analysis a Hind III fragment of about 7,5 kb was subcloned in a likewise restricted vector (Bluescript SK, Stratagene #212206). This plasmid, called SKL 52 (H3) MP12, was also deposited by the DSM (# 7353). Sequence information derived from this clone is shown in SEQ ID NO: 1. At nucleotide No. 1050, the determined cDNA and the respective genomic sequence differ by one basepair (cDNA: G; genomic DNA: A). We assume the genomic sequence to be correct, as it was confirmed also by sequencing of the amplified genomic DNA from embryonic tissue which had been used for the mRNA preparation. The genomic DNA contains an intron of about 2 kb between basepairs 332 and 333 of SEQ ID NO: 1. The sequence of the intron is not shown. The correct exon/exon junction was confirmed by sequencing an amplification product derived from cDNA which comprises this region. This sequencing information was obtained by the help of a slightly modified method described in detail by Frohman (Amplifications, published by Perkin-Elmer Corporation, issue 5 (1990), pp 11-15). The same embryo RNA which was used for the isolation of the 3' end of MP-52 was reverse transcribed using an internal primer of the MP-52 sequence oriented in the 5' direction (ACAGCAGGTGGGTGGTGTGGACT). A polyA tail was appended to the 5' end of the first strand cDNA by using terminal transferase. A two step amplification was performed first by application of a primer consisting of oligo dT and an adaptor primer (AGAATTCGCATGCCATGGTCGACGAAGC(T_{16})) and secondly an

adaptor primer (AGAATTCGCATGCCATGGTCGACG) and an internal primer (CCAGCAGCCCATCCTTCTCC) of the MP-52 sequence. The amplification products were reamplified using the same adaptor primer and a nested internal primer (TCCAGGGCACTAATGTCAAACACG) of the MP-52 sequence. Consecutively the reamplification products were again reamplified using a nested adaptor primer (ATTCGCATGCCATGGTCGACGAAG) and a nested internal primer (ACTAATGTCAAACACGTACCTCTG) of the MP-52 sequence. The final reamplification products were blunt end cloned in a vector (Bluescript SK, Stratagene #212206) restricted with EcoRV. Clones were characterized by their sequence overlap to the DNA of λ 2.7.4.

Plasmid SKL 52 (H3) MP12 was deposited under number 7353 at DSM (Deutsche Sammlung von Mikroorganismen und Zellkulturen), Mascheroder Weg 1b, 3300 Braunschweig, on 10.12.1992.

Phage λ 2.7.4. was deposited under number 7387 at DSM on 13.1.1993.

Claims

1. A DNA sequence encoding a protein of the TGF-ß family selected from the following group:

(a) a DNA sequence comprising the nucleotides

ATGAACTCCATGGACCCCGAGTCCACA

with the reading frame for the protein starting at the first nucleotide

(b) a DNA sequence comprising the nucleotides

CTTCTCAAGGCCAACACAGCTGCAGGCACC

with the reading frame for the protein starting at the first nucleotide

(c) DNA sequences which are degenerate as a result of the genetic code to the DNA sequences of (a) and (b)

(d) allelic derivatives of the DNA sequences of (a) and (b)

(e) DNA sequences hybridizing to the DNA sequences in (a), (b), (c) or (d) and encoding a protein containing the aminoacid sequence

Met-Asn-Ser-Met-Asp-Pro-Glu-Ser-Thr

or

Leu-Leu-Lys-Ala-Asn-Thr-Ala-Ala-Gly-Thr

(f) DNA sequences hybridizing to the DNA sequences in (a), (b), (c) and (d) and encoding a protein having essentially the same biological properties.

2. The DNA sequence according to claim 1 which is a vertebrate DNA sequence, a mammalian DNA sequence, preferably a primate, human, porcine, bovine, or rodent DNA sequence, and preferably including a rat and a mouse DNA sequence.

3. The DNA sequence according to claim 1 or 2 which is a DNA sequence comprising the nucleotides as shown in SEQ ID NO. 1.

4. The DNA sequence according to claim 1 or 2 which is a DNA sequence comprising the nucleotides as shown in SEQ ID NO. 2.

5. The DNA sequence according to claim 1 or 2 which is a DNA sequence comprising the nucleotides as shown in SEQ ID NO. 5.

6. The DNA sequence according to claim 1 or 2 which is a DNA sequence comprising the nucleotides as shown in SEQ ID NO. 6.

7. A recombinant DNA molecule comprising a DNA sequence according to any one of claims 1 to 6.

8. The recombinant DNA molecule according to claim 7 in which said DNA sequence is functionally linked to an expression-control sequence.

9. A host containing a recombinant DNA molecule according to claim 7 or 8.

10. The host according to claim 9 which is a bacterium, a fungus, a plant cell or an animal cell.

11. A process for the production of a protein of the TGF-ß family comprising cultivating a host according to claim 9 or 10 and recovering said TGF-ß protein from the culture.

12. A protein of the TGF-ß family encoded by a DNA sequence according to any one of claims 1 to 4 or a fragment thereof encoded by a DNA-sequence according to claim 5 or 6.

13. A protein according to claim 12 comprising the amino acid sequence of SEQ ID NO: 3.

14. A protein according to claim 12 comprising the amino acid sequence of SEQ ID NO. 4.

15. A pharmaceutical composition containing a protein of the TGF-ß family according to any one of claims 12 to 14, optionally in combination with a pharmaceutically acceptable carrier.

16. The pharmaceutical composition according to claim 15 for the treatment or prevention of bone, cartilage, connective tissue, skin, mucous membrane, endothelial, epithelial, neuronal, renal or tooth defects, for use in the case of dental implants, for use in wound healing or tissue repair processes, as a morphogenic factor used for inducing liver tissue growth, induction of the proliferation of precursor cells or bone marrow cells, for maintaining a differentiated state and for the treatment of impaired fertility or for contraception.

17. An antibody or antibody fragment which is capable of specifically binding to a protein of claims 12, 13 or 14.

18. Antibody or antibody fragment according to claim 17 which is a monoclonal antibody.

19. Use of an antibody or antibody fragment according to claims 17 or 18 for diagnostic methods.

Abstract

The invention provides DNA sequences encoding novel members of the TGF-ß family of proteins. The TGF-ß family comprises proteins which function as growth and/or differentiation factors and which are useful in medical applications. Accordingly, the invention also describes the isolation of the above-mentioned DNA sequences, the expression of the encoded proteins, the production of said proteins and pharmaceutical compositions containing said proteins.

Fig.1a

```
                    10          20          30          40          50
MP 52   CSRKALHVNF  KDMGWDDWII  APLEYEAFHC  EGLCEFPLRS  HLEPTNHAVI

BMP 2   CKRHPLYVDF  SDVGWNDWIV  APPGYHAFYC  HGECPFPLAD  HLNSTNHAIV

BMP 4   CRRHSLYVDF  SDVGWNDWIV  APPGYQAFYC  HGDCPFPLAD  HLNSTNHAIV

BMP 5   CKKHELYVSF  RDLGWQDWII  APEGYAAFYC  DGECSFPLNA  HMNATNHAIV

BMP 6   CRKHELYVSF  QDLGWQDWII  APKGYAANYC  DGECSFPLNA  HMNATNHAIV

BMP 7   CKKHELYVSF  RDLGWQDWII  APEGYAAYYC  EGECAFPLNS  YMNATNHAIV
          * +  * * *   * ** ***+ **  * *+ * +* * *** + ++  ****

                    60          70          80          90          100
MP 52   QTLMNSMDPE  STPPTCCVPT  RLSPISILFI  DSANNVVYKQ  YEDMVVESCG  CR

BMP 2   QTLVNSVNS-  KIPKACCVPT  ELSAISMLYL  DENEKVVLKN  YQDMVVEGCG  CR

BMP 4   QTLVNSVNS-  SIPKACCVPT  ELSAISMLYL  DEYDKVVLKN  YQEMVVEGCG  CR

BMP 5   QTLVHLMFPD  HVPKPCCAPT  KLNAISVLYF  DDSSNVILKK  YRNMVVRSCG  CH

BMP 6   QTLVHLMNPE  YVPKPCCAPT  KLNAISVLYF  DDNSNVILKK  YRNMVVRACG  CH

BMP 7   QTLVHFINPE  TVPKPCCAPT  QLNAISVLYF  DDSSNVILKK  YRNMVVRACG  CH
          *** +++ ++  + *  **+**  *+ ** *   *  +*+ *  * +***++** *+
```

Fig.1b

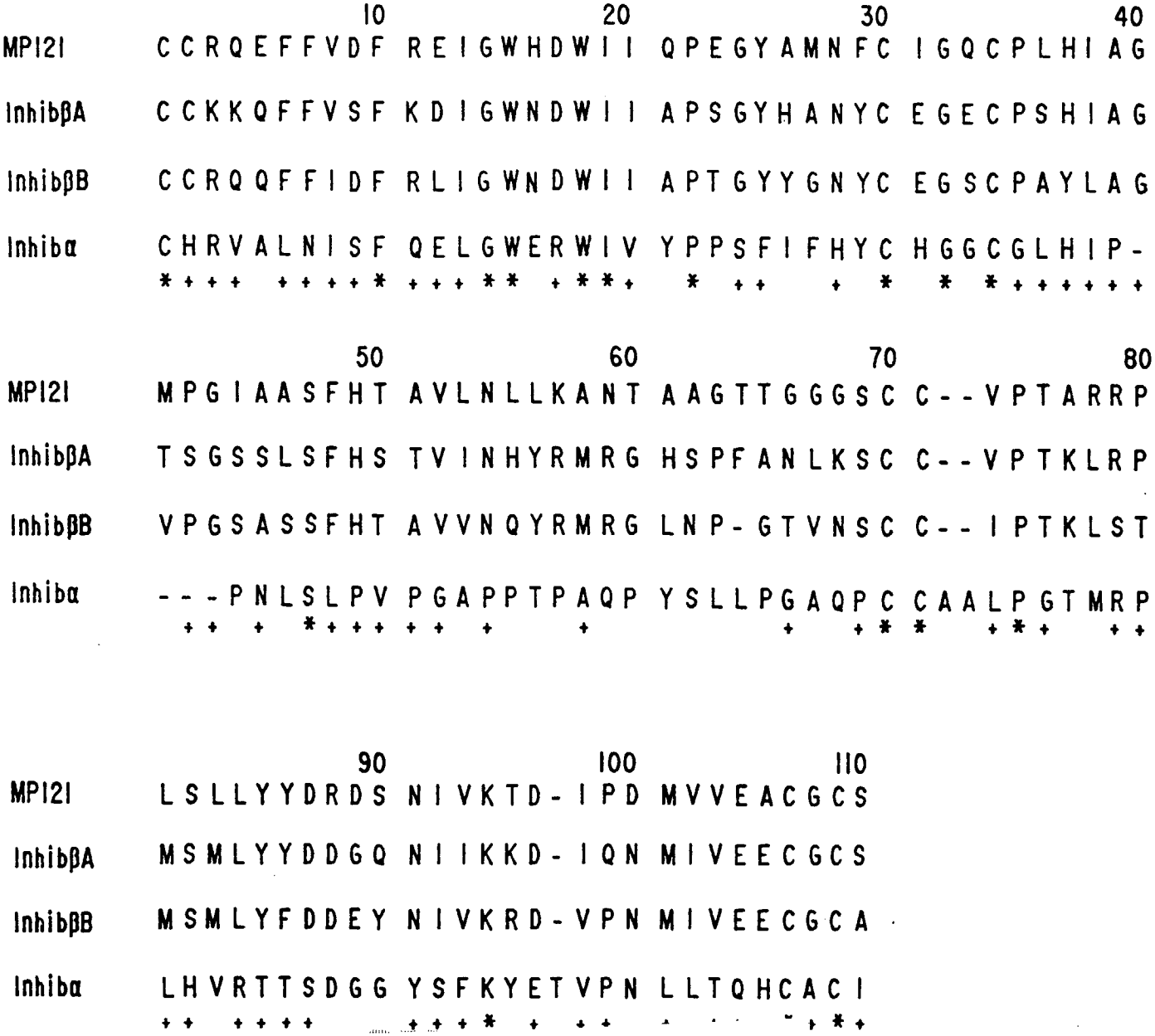


Fig.2a

	Eco RI Nco I
OD	ATGAATTCCCATGGACCTGGGCTGGMAKGAMTGGAT
BMP 2	ACGTGGGGTGGAATGACTGGAT
BMP 3	ATATTGGCTGGAGTGAATGGAT
BMP 4	ATGTGGGCTGGAATGACTGGAT
BMP 7	ACCTGGGCTGGCAGGACTGGAT
TGF-βI	AGGACCTCGGCTGGAAGTGGAT
TGF-β2	GGGATCTAGGGTGGAAATGGAT
TGF-β3	AGGATCTGGGCTGGAAGTGGGT
inhibin α	AGCTGGGCTGGGAACGGTGGAT
inhibin βA	ACATCGGCTGGAATGACTGGAT
inhibin βB	TCATCGGCTGGAACGACTGGAT

Fig.2b

	Eco RI
OID	ATGAATTCGAGCTGCGTSGGSRCACAGCA
BMP 2	GAGTTCTGTCGGGACACAGCA
BMP 3	CATCTTTTCTGGTACACAGCA
BMP 4	CAGTTCAGTGGGCACACAACA
BMP 7	GAGCTGCGTGGGCGCACAGCA
TGF-βI	CAGCGCCTGCGGCACGCAGCA
TGF-β2	TAAATCTTGGGACACGCAGCA
TGF-β3	CAGGTCCTGGGGCACGCAGCA
inhibin α	CCCTGGGAGAGCAGCACAGCA
inhibin βA	CAGCTTGGTGGGCACACAGCA
inhibin βB	CAGCTTGGTGGGAATGCAGCA

SEQ ID NO. 1

SEQUENCE TYPE: Nucleic Acid
SEQUENCE LENGTH: 1207 Base Pairs

STRANDEDNESS: Double or Single
TOPOLOGY: Linear
MOLECULAR TYPE: DNA or cDNA from mRNA

ORIGINAL SOURCE: -
ORGANISM: Human
IMMEDIATE EXPERIMENTAL SOURCE: Embryo Tissue

PROPERTIES: Sequence Coding for Human TGF-ß-like Protein (MP-52)

```
ACCGGGCGGC CCTGAACCCA AGCCAGGACA CCCTCCCCAA ACAAGGCAGG CTACAGCCCG        60

GACTGTGACC CCAAAAGGAC AGCTTCCCGG AGGCAAGGCA CCCCCAAAAG CAGGATCTGT       120

CCCCAGCTCC TTCCTGCTGA AGAAGGCCAG GGAGCCCGGG CCCCCACGAG AGCCCAAGGA       180

GCCGTTTCGC CCACCCCCCA TCACACCCCA CGAGTACATG CTCTCGCTGT ACAGGACGCT       240

GTCCGATGCT GACAGAAAGG GAGGCAACAG CAGCGTGAAG TTGGAGGCTG GCCTGGCCAA       300

CACCATCACC AGCTTTATTG ACAAAGGGCA AGATGACCGA GGTCCCGTGG TCAGGAAGCA       360

GAGGTACGTG TTTGACATTA GTGCCCTGGA GAAGGATGGG CTGCTGGGGG CCGAGCTGCG       420

GATCTTGCGG AAGAAGCCCT CGGACACGGC CAAGCCAGCG GCCCCCGGAG GCGGGCGGGC       480

TGCCCAGCTG AAGCTGTCCA GCTGCCCCAG CGGCCGGCAG CCGGCCTCCT TGCTGGATGT       540

GCGCTCCGTG CCAGGCCTGG ACGGATCTGG CTGGGAGGTG TTCGACATCT GGAAGCTCTT       600

CCGAAACTTT AAGAACTCGG CCCAGCTGTG CCTGGAGCTG GAGGCCTGGG AACGGGGCAG       660

GGCCGTGGAC CTCCGTGGCC TGGGCTTCGA CCGCGCCGCC CGGCAGGTCC ACGAGAAGGC       720

CCTGTTCCTG GTGTTTGGCC GCACCAAGAA ACGGGACCTG TTCTTTAATG AGATTAAGGC       780

CCGCTCTGGC CAGGACGATA AGACCGTGTA TGAGTACCTG TTCAGCCAGC GGCGAAAACG       840

GCGGGCCCCA CTGGCCACTC GCCAGGGCAA GCGACCCAGC AAGAACCTTA AGGCTCGCTG       900

CAGTCGGAAG GCACTGCATG TCAACTTCAA GGACATGGGC TGGGACGACT GGATCATCGC       960

ACCCCTTGAG TACGAGGCTT TCCACTGCGA GGGGCTGTGC GAGTTCCCAT TGCGCTCCCA      1020

CCTGGAGCCC ACGAATCATG CAGTCATCCA GACCCTGATG AACTCCATGG ACCCCGAGTC      1080

CACACCACCC ACCTGCTGTG TGCCCACGCG GCTGAGTCCC ATCAGCATCC TCTTCATTGA      1140

CTCTGCCAAC AACGTGGTGT ATAAGCAGTA TGAGGACATG GTCGTGGAGT CGTGTGGCTG      1200

CAGGTAG                                                                1207
```

SEQ ID NO.2

SEQUENCE TYPE: Nucleic Acid
SEQUENCE LENGTH: 2272 Base Pairs

STRANDEDNESS: Double or Single
TOPOLOGY: Linear
MOLECULAR TYPE: cDNA from mRNA

ORIGINAL SOURCE: -
ORGANISM: Human
IMMEDIATE EXPERIMENTAL SOURCE: Liver Tissue

PROPERTIES: Sequence Coding for Human TGF-ß-like Protein (MP-121)

```
CAAGGAGCCA TGCCAGCTGG ACACACACTT CTTCCAGGGC CTCTGGCAGC CAGGACAGAG    60
TTGAGACCAC AGCTGTTGAG ACCCTGAGCC CTGAGTCTGT ATTGCTCAAG AAGGGCCTTC   120
CCCAGCAATG ACCTCCTCAT TGCTTCTGGC CTTTCTCCTC CTGGCTCCAA CCACAGTGGC   180
CACTCCCAGA GCTGGCGGTC AGTGTCCAGC ATGTGGGGGG CCCACCTTGG AACTGGAGAG   240
CCAGCGGGAG CTGCTTCTTG ATCTGGCCAA GAGAAGCATC TTGGACAAGC TGCACCTCAC   300
CCAGCGCCCA ACACTGAACC GCCCTGTGTC CAGAGCTGCT TTGAGGACTG CACTGCAGCA   360
CCTCCACGGG GTCCCACAGG GGGCACTTCT AGAGGACAAC AGGGAACAGG AATGTGAAAT   420
CATCAGCTTT GCTGAGACAG GCCTCTCCAC CATCAACCAG ACTCGTCTTG ATTTTCACTT   480
CTCCTCTGAT AGAACTGCTG GTGACAGGGA GGTCCAGCAG GCCAGTCTCA TGTTCTTTGT   540
GCAGCTCCCT TCCAATACCA CTTGGACCTT GAAAGTGAGA GTCCTTGTGC TGGGTCCACA   600
TAATACCAAC CTCACCTTGG CTACTCAGTA CCTGCTGGAG GTGGATGCCA GTGGCTGGCA   660
TCAACTCCCC CTAGGGCCTG AAGCTCAAGC TGCCTGCAGC CAGGGGCACC TGACCCTGGA   720
GCTGGTACTT GAAGGCCAGG TAGCCCAGAG CTCAGTCATC CTGGGTGGAG CTGCCCATAG   780
GCCTTTTGTG GCAGCCCGGG TGAGAGTTGG GGGCAAACAC CAGATTCACC GACGAGGCAT   840
CGACTGCCAA GGAGGGTCCA GGATGTGCTG TCGACAAGAG TTTTTTGTGG ACTTCCGTGA   900
GATTGGCTGG CACGACTGGA TCATCCAGCC TGAGGGCTAC GCCATGAACT TCTGCATAGG   960
GCAGTGCCCA CTACACATAG CAGGCATGCC TGGTATTGCT GCCTCCTTTC ACACTGCAGT  1020
GCTCAATCTT CTCAAGGCCA ACACAGCTGC AGGCACCACT GGAGGGGGCT CATGCTGTGT  1080
ACCCACGGCC CGGCGCCCCC TGTCTCTGCT CTATTATGAC AGGGACAGCA ACATTGTCAA  1140
GACTGACATA CCTGACATGG TAGTAGAGGC CTGTGGGTGC AGTTAGTCTA TGTGTGGTAT  1200
GGGCAGCCCA AGGTTGCATG GGAAAACACG CCCCTACAGA AGTGCACTTC CTTGAGAGGA  1260
GGGAATGACC TCATTCTCTG TCCAGAATGT GGACTCCCTC TTCCTGAGCA TCTTATGGAA  1320
ATTACCCCAC CTTTGACTTG AAGAAACCTT CATCTAAAGC AAGTCACTGT GCCATCTTCC  1380
TGACCACTAC CCTCTTTCCT AGGGCATAGT CCATCCCGCT AGTCCATCCC GCTAGCCCCA  1440
```

CTCCAGGGAC TCAGACCCAT CTCCAACCAT GAGCAATGCC ATCTGGTTCC CAGGCAAAGA 1500

CACCCTTAGC TCACCTTTAA TAGACCCCAT AACCCACTAT GCCTTCCTGT CCTTTCTACT 1560

CAATGGTCCC CACTCCAAGA TGAGTTGACA CAACCCCTTC CCCCAATTTT TGTGGATCTC 1620

CAGAGAGGCC CTTCTTTGGA TTCACCAAAG TTTAGATCAC TGCTGCCCAA AATAGAGGCT 1680

TACCTACCCC CCTCTTTGTT GTGAGCCCCT GTCCTTCTTA GTTGTCCAGG TGAACTACTA 1740

AAGCTCTCTT TGCATACCTT CATCCATTTT TTGTCCTTCT CTGCCTTTCT CTATGCCCTT 1800

AAGGGGTGAC TTGCCTGAGC TCTATCACCT GAGCTCCCCT GCCCTCTGGC TTCCTGCTGA 1860

GGTCAGGGCA TTTCTTATCC CTGTTCCCTC TCTGTCTAGG TGTCATGGTT CTGTGTAACT 1920

GTGGCTATTC TGTGTCCCTA CACTACCTGG CTACCCCCTT CCATGGCCCC AGCTCTGCCT 1980

ACATTCTGAT TTTTTTTTTT TTTTTTTTTT TGAAAAGTTA AAAATTCCTT AATTTTTTAT 2040

TCCTGGTACC ACTACCACAA TTTACAGGGC AATATACCTG ATGTAATGAA AAGAAAAAGA 2100

AAAAGACAAA GCTACAACAG ATAAAAGACC TCAGGAATGT ACATCTAATT GACACTACAT 2160

TGCATTAATC AATAGCTGCA CTTTTTGCAA ACTGTGGCTA TGACAGTCCT GAACAAGAAG 2220

GGTTTCCTGT TTAAGCTGCA GTAACTTTTC TGACTATGGA TCATCGTTCC TT 2272

SEQ ID NO. 3

SEQUENCE TYPE: Amino Acid
SEQUENCE LENGTH: 401 Amino Acids

ORIGINAL SOURCE: -
ORGANISM: Human
IMMEDIATE EXPERIMENTAL SOURCE: Embryo Tissue

PROPERTIES: Human TGF-ß-like Protein (MP-52)

```
PGGPEPKPGH PPQTRQATAR TVTPKGQLPG GKAPPKAGSV PSSFLLKKAR EPGPPREPKE    60
PFRPPPITPH EYMLSLYRTL SDADRKGGNS SVKLEAGLAN TITSFIDKGQ DDRGPVVRKQ   120
RYVFDISALE KDGLLGAELR ILRKKPSDTA KPAAPGGGRA AQLKLSSCPS GRQPASLLDV   180
RSVPGLDGSG WEVFDIWKLF RNFKNSAQLC LELEAWERGR AVDLRGLGFD RAARQVHEKA   240
LFLVFGRTKK RDLFFNEIKA RSGQDDKTVY EYLFSQRRKR RAPLATRQGK RPSKNLKARC   300
SRKALHVNFK DMGWDDWIIA PLEYEAFHCE GLCEFPLRSH LEPTNHAVIQ TLMNSMDPES   360
TPPTCCVPTR LSPISILFID SANNVVYKQY EDMVVESCGC R                       401
```

SEQ ID NO. 4

SEQUENCE TYPE: Amino Acid
SEQUENCE LENGTH: 352 Amino Acids

ORIGINAL SOURCE: -
ORGANISM: Human

PROPERTIES: Human TGF-ß-like Protein (MP-121)

```
MTSSLLLAFL LLAPTTVATP RAGGQCPACG GPTLELESQR ELLLDLAKRS ILDKLHLTQR    60
PTLNRPVSRA ALRTALQHLH GVPQGALLED NREQECEIIS FAETGLSTIN QTRLDFHFSS   120
DRTAGDREVQ QASLMFFVQL PSNTTWTLKV RVLVLGPHNT NLTLATQYLL EVDASGWHQL   180
PLGPEAQAAC SQGHLTLELV LEGQVAQSSV ILGGAAHRPF VAARVRVGGK HQIHRRGIDC   240
QGGSRMCCRQ EFFVDFREIG WHDWIIQPEG YAMNFCIGQC PLHIAGMPGI AASFHTAVLN   300
LLKANTAAGT TGGGSCCVPT ARRPLSLLYY DRDSNIVKTD IPDMVVEACG CS           352
```

SEQ ID NO. 5

SEQUENCE TYPE: Nucleic Acid
SEQUENCE LENGTH: 265 Base Pairs

STRANDEDNESS: Double or Single
TOPOLOGY: Linear
MOLECULAR TYPE: cDNA from mRNA

ORIGINAL SOURCE: -
ORGANISM: Human
IMMEDIATE EXPERIMENTAL SOURCE: Liver Tissue

PROPERTIES: Sequence coding for a Part of the Mature Human TGF-ß-like Protein (MP-121)

```
CATCCAGCCT GAGGGCTACG CCATGAACTT CTGCATAGGG CAGTGCCCAC TACACATAGC      60

AGGCATGCCT GGTATTGCTG CCTCCTTTCA CACTGCAGTG CTCAATCTTC TCAAGGCCAA     120

CACAGCTGCA GGCACCACTG GAGGGGGCTC ATGCTGTGTA CCCACGGCCC GGCGCCCCCT     180

GTCTCTGCTC TATTATGACA GGGACAGCAA CATTGTCAAG ACTGACATAC CTGACATGGT     240

AGTAGAGGCC TGTGGGTGCA GTTAG                                           265
```

SEQ ID NO. 6

SEQUENCE TYPE: Nucleic Acid
SEQUENCE LENGTH: 139 Base Pairs

STRANDEDNESS: Double or Single
TOPOLOGY: Linear
MOLECULAR TYPE: cDNA from mRNA

ORIGINAL SOURCE: -
ORGANISM: Human
IMMEDIATE EXPERIMENTAL SOURCE: Embryo Tissue

PROPERTIES: Sequence Coding for a Part of the Mature Human TGF-ß-like Protein (MP-52)

CATCGCACCC CTTGAGTACG AGGCTTTCCA CTGCGAGGGG CTGTGCGAGT TCCCATTGCG 60

CTCCCACCTG GAGCCCACGA ATCATGCAGT CATCCAGACC CTGATGAACT CCATGGACCC 120

CGAGTCCACA CCACCCACC 139

Figure 1a

```
                10          20          30          40          50
MP 52   CSRKALHVNF KDMGWDDWII APLEYEAFHC EGLCEFPLRS HLEPTNHAVI

BMP 2   CKRHPLYVDF SDVGWNDWIV APPGYHAFYC HGECPFPLAD HLNSTNHAIV

BMP 4   CRRHSLYVDF SDVGWNDWIV APPGYQAFYC HGDCPFPLAD HLNSTNHAIV

BMP 5   CKKHELYVSF RDLGWQDWII APEGYAAFYC DGECSFPLNA HMNATNHAIV

BMP 6   CRKHELYVSF QDLGWQDWII APKGYAANYC DGECSFPLNA HMNATNHAIV

BMP 7   CKKHELYVSF RDLGWQDWII APEGYAAYYC EGECAFPLNS YMNATNHAIV
        * +  * * *  * ** ***+ **  * *+ * +* * *** + ++  ****


                60          70          80          90          100
MP 52   QTLMNSMDPE STPPTCCVPT RLSPISILFI DSANNVVYKQ YEDMVVESCG  CR

BMP 2   QTLVNSVNS- KIPKACCVPT ELSAISMLYL DENEKVVLKN YQDMVVEGCG  CR

BMP 4   QTLVNSVNS- SIPKACCVPT ELSAISMLYL DEYDKVVLKN YQEMVVEGCG  CR

BMP 5   QTLVHLMFPD HVPKPCCAPT KLNAISVLYF DDSSNVILKK YRNMVVRSCG  CH

BMP 6   QTLVHLMNPE YVPKPCCAPT KLNAISVLYF DDNSNVILKK YRNMVVRACG  CH

BMP 7   QTLVHFINPE TVPKPCCAPT QLNAISVLYF DDSSNVILKK YRNMVVRACG  CH

        *** +++ ++ + *  **+**  *+ ** *   *   +*+ *  * +***++**  *+
```

Figur 1b

```
                          10                  20                  30                  40
MP121      C C R Q E F F V D F  R E I G W H D W I I  Q P E G Y A M N F C  I G Q C P L H I A G
InhibβA    C C K K Q F F V S F  K D I G W N D W I I  A P S G Y H A N Y C  E G E C P S H I A G
InhibβB    C C R Q Q F F I D F  R L I G W N D W I I  A P T G Y Y G N Y C  E G S C P A Y L A G
Inhibα     C H R V A L N I S F  Q E L G W E R W I V  Y P P S F I F H Y C  H G G C G L H I P -
           * + + +  + + + + *  + + + * *  + * * +  * + +  + * * * + + + + + +

                          50                  60                  70                  80
MP121      M P G I A A S F H T  A V L N L L K A N T  A A G T T G G G S C  C - - V P T A R R P
InhibβA    T S G S S L S F H S  T V I N H Y R M R G  H S P F A N L K S C  C - - V P T K L R P
InhibβB    V P G S A S S F H T  A V V N Q Y R M R G  L N P - G T V N S C  C - - I P T K L S T
Inhibα     - - - P N L S L P V  P G A P P T P A Q P  Y S L L P G A Q P C  C A A L P G T M R P
             + +  +  * + + +  + +  +     +           +    + * *  *    + * +    + +

                          90                  100                 110
MP121      L S L L Y Y D R D S  N I V K T D - I P D  M V V E A C G C S
InhibβA    M S M L Y Y D D G Q  N I I K K D - I Q N  M I V E E C G C S
InhibβB    M S M L Y F D D E Y  N I V K R D - V P N  M I V E E C G C A
Inhibα     L H V R T T S D G G  Y S F K Y E T V P N  L L T Q H C A C I
           + +  + + + +       + + + *  +  + +   +  + +  * + * +
```

Figure 2a

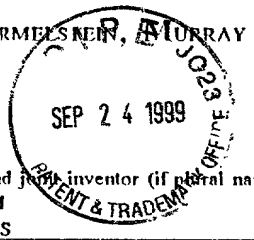
	Eco RI Nco I
OD	ATGAATTCCCATGGACCTGGGCTGGMAKGAMTGGAT
BMP 2	ACGTGGGGTGGAATGACTGGAT
BMP 3	ATATTGGCTGGAGTGAATGGAT
BMP 4	ATGTGGGCTGGAATGACTGGAT
BMP 7	ACCTGGGCTGGCAGGACTGGAT
TGF-ß1	AGGACCTCGGCTGGAAGTGGAT
TGF-ß2	GGGATCTAGGGTGGAAATGGAT
TGF-ß3	AGGATCTGGGCTGGAAGTGGGT
inhibin α	AGCTGGGCTGGGAACGGTGGAT
inhibin $ß_A$	ACATCGGCTGGAATGACTGGAT
inhibin $ß_B$	TCATCGGCTGGAACGACTGGAT

Figure 2b

	Eco RI
OID	ATGAATTCGAGCTGCGTSGGSRCACAGCA
BMP 2	GAGTTCTGTCGGGACACAGCA
BMP 3	CATCTTTTCTGGTACACAGCA
BMP 4	CAGTTCAGTGGGCACACAACA
BMP 7	GAGCTGCGTGGGCGCACAGCA
TGF-ß1	CAGCGCCTGCGGCACGCAGCA
TGF-ß2	TAAATCTTGGGACACGCAGCA
TGF-ß3	CAGGTCCTGGGGCACGCAGCA
inhibin α	CCCTGGGAGAGCAGCACAGCA
inhibin $ß_A$	CAGCTTGGTGGGCACACAGCA
inhibin $ß_B$	CAGCTTGGTGGGAATGCAGCA

N, M, M & O Docket No. 64-4017 NIKAIDO, MARMELSTEIN, MURRAY & ORAM

Declaration For U.S. Patent Application



As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled (Insert Title) DNA SEQUENCES ENCODING NOVEL GROWTH/DIFFERENTIATION FACTORS the specification of which

(Check one of blocks 1, 2 or 3. See note A on back of this page)

1. ☐ is attached hereto.
2. ☐ was filed on _____ as International PCT Application Serial No. _____ and was amended on _____. (if applicable)
3. ☒ was filed on August 12, 1994 as U.S. Application Serial No. 08/289,222 and was amended on _____. (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application for which priority is claimed:

				Priority Claimed
(List prior foreign applications. See note B on back of this page)	92 102 324.8 (Number)	Europe (Country)	12/2/92 (Day/Month/Year Filed)	☒ Yes ☐ No
	P 44 23 190.3 (Number)	DE (Country)	1/7/94 (Day/Month/Year Filed)	☒ Yes ☐ No
	(Number)	(Country)	(Day/Month/Year Filed)	☐ Yes ☐ No
	(Number)	(Country)	(Day/Month/Year Filed)	☐ Yes ☐ No

(See Note C on back of this page) ☐ See attached list for additional prior foreign applications

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT International application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT International filing date of this application:

(List prior U.S. Applications or P C T International applications designating the U.S.)	PCT/EP93/00350 (Application Serial No.)	12/2/93 (Filing Date)	Pending (Status) (patented, pending, abandoned)
	(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

And I hereby appoint as principal attorneys David T. Nikaido, Reg. No. 22,663; Charles M. Marmelstein, Reg. No. 25,895; George E. Oram, Jr., Reg. No. 27,931; Robert B. Murray, Reg. No. 22,980; Martin S. Postman, Reg. No. 18,570; E. Marcie Emas, Reg. No. 32,131; Michael G. Gilman, Reg. No. 19,114, Douglas H. Goldhush, Reg. No. 33,125; Kevin C. Brown, Reg. No. 32,402; Monica Chin Kitts, Reg. No. 36,105; Sharon L. Nolan, Reg. No. 36,335, and John R. Fuisz, Reg. No. 37,327.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

(See Note D on back of this page)

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Inventor's signature
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Citizenship

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Post Office Address

Full name of seventh joint inventor, if any

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Citizenship

Post Office Address

48
N2 M

SEQUENCE LISTING

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(ii) TITLE OF INVENTION: GROWTH/DIFFERENTIATION FACTORS OF THE TGF-B FAMILY

(iii) NUMBER OF SEQUENCES: 53

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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: UNKNOWN
(B) FILING DATE: 25-AUG-1999
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: US 08/289,222
(B) FILING DATE: 12-AUG-1994

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: DE P 44 23 190.3
(B) FILING DATE: 07-JUL-1994

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: EPO 92102324.8
(B) FILING DATE: 12-FEB-1992

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: PCT/EP93/00350
(B) FILING DATE: 12-FEB-1993

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(B) TELEFAX: 202/638-4810

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1207 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA or cDNA from mRNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

ACCGGGCGGC CCTGAACCCA AGCCAGGACA CCCTCCCCAA ACAAGGCAGG CTACAGCCCG 60

GACTGTGACC CCAAAAGGAC AGCTTCCCGG AGGCAAGGCA CCCCCAAAAG CAGGATCTGT 120

GCCCAGCTCC TTCCTGCTGA AGAAGGCCAG GGAGCCCGGG CCCCCACGAG AGCCCAAGGA 180

GCCGTTTCGC CCACCCCCCA TCACACCCCA CGAGTACATG CTCTCGCTGT ACAGGACGCT 240

GTCCGATGCT GACAGAAAGG GAGGCAACAG CAGCGTGAAG TTGGAGGCTG GCCTGGCCAA 300

CACCATCACC AGCTTTATTG ACAAAGGGCA AGATGACCGA GGTCCCGTGG TCAGGAAGCA 360

GAGGTACGTG TTTGACATTA GTGCCCTGGA GAAGGATGGG CTGCTGGGGG CCGAGCTGCG 420

GATCTTGCGG AAGAAGCCCT CGGACACGGC CAAGCCAGCG GCCCCCGGAG GCGGGCGGGC 480

TGCCCAGCTG AAGCTGTCCA GCTGCCCCAG CGGCCGGCAG CCGGCCTCCT TGCTGGATGT 540

GCGCTCCGTG CCAGGCCTGG ACGGATCTGG CTGGGAGGTG TTCGACATCT GGAAGCTCTT 600

CCGAAACTTT AAGAACTCGG CCCAGCTGTG CCTGGAGCTG GAGGCCTGGG AACGGGGCAG 660

GGCCGTGGAC CTCCGTGGCC TGGGCTTCGA CCGCGCCGCC CGGCAGGTCC ACGAGAAGGC 720

CCTGTTCCTG GTGTTTGGCC GCACCAAGAA ACGGGACCTG TTCTTTAATG AGATTAAGGC 780

CCGCTCTGGC CAGGACGATA AGACCGTGTA TGAGTACCTG TTCAGCCAGC GGCGAAAACG 840

GCGGGCCCCA CTGGCCACTC GCCAGGGCAA GCGACCCAGC AAGAACCTTA AGGCTCGCTG 900

CAGTCGGAAG GCACTGCATG TCAACTTCAA GGACATGGGC TGGGACGACT GGATCATCGC 960

ACCCCTTGAG TACGAGGCTT TCCACTGCGA GGGGCTGTGC GAGTTCCCAT TGCGCTCCCA 1020

CCTGGAGCCC ACGAATCATG CAGTCATCCA GACCCTGATG AACTCCATGG ACCCCGAGTC 1080

CACACCACCC ACCTGCTGTG TGCCCACGCG GCTGAGTCCC ATCAGCATCC TCTTCATTGA 1140

CTCTGCCAAC AACGTGGTGT ATAAGCAGTA TGAGGACATG GTCGTGGAGT CGTGTGGCTG 1200

CAGGTAG 1207

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2272 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA from mRNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

CAAGGAGCCA TGCCAGCTGG ACACACACTT CTTCCAGGGC CTCTGGCAGC CAGGACAGAG 60

TTGAGACCAC AGCTGTTGAG ACCCTGAGCC CTGAGTCTGT ATTGCTCAAG AAGGGCCTTC 120

CCCAGCAATG ACCTCCTCAT TGCTTCTGGC CTTTCTCCTC CTGGCTCCAA CCACAGTGGC 180

CACTCCCAGA GCTGGCGGTC AGTGTCCAGC ATGTGGGGGG CCCACCTTGG AACTGGAGAG 240

CCAGCGGGAG CTGCTTCTTG ATCTGGCCAA GAGAAGCATC TTGGACAAGC TGCACCTCAC 300

CCAGCGCCCA ACACTGAACC GCCCTGTGTC CAGAGCTGCT TTGAGGACTG CACTGCAGCA 360

CCTCCACGGG GTCCCACAGG GGGCACTTCT AGAGGACAAC AGGGAACAGG AATGTGAAAT 420

CATCAGCTTT GCTGAGACAG GCCTCTCCAC CATCAACCAG ACTCGTCTTG ATTTTCACTT 480

CTCCTCTGAT AGAACTGCTG GTGACAGGGA GGTCCAGCAG GCCAGTCTCA TGTTCTTTGT 540

GCAGCTCCCT TCCAATACCA CTTGGACCTT GAAAGTGAGA GTCCTTGTGC TGGGTCCACA 600

TAATACCAAC CTCACCTTGG CTACTCAGTA CCTGCTGGAG GTGGATGCCA GTGGCTGGCA 660

TCAACTCCCC CTAGGGCCTG AAGCTCAAGC TGCCTGCAGC CAGGGGCACC TGACCCTGGA 720

GCTGGTACTT GAAGGCCAGG TAGCCCAGAG CTCAGTCATC CTGGGTGGAG CTGCCCATAG 780

GCCTTTTGTG GCAGCCCGGG TGAGAGTTGG GGGCAAACAC CAGATTCACC GACGAGGCAT 840

CGACTGCCAA GGAGGGTCCA GGATGTGCTG TCGACAAGAG TTTTTTGTGG ACTTCCGTGA 900

GATTGGCTGG CACGACTGGA TCATCCAGCC TGAGGGCTAC GCCATGAACT TCTGCATAGG 960

GCAGTGCCCA CTACACATAG CAGGCATGCC TGGTATTGCT GCCTCCTTTC ACACTGCAGT 1020

GCTCAATCTT CTCAAGGCCA ACACAGCTGC AGGCACCACT GGAGGGGGCT CATGCTGTGT 1080

ACCCACGGCC CGGCGCCCCC TGTCTCTGCT CTATTATGAC AGGGACAGCA ACATTGTCAA 1140

GACTGACATA CCTGACATGG TAGTAGAGGC CTGTGGGTGC AGTTAGTCTA TGTGTGGTAT 1200

GGGCAGCCCA AGGTTGCATG GGAAAACACG CCCCTACAGA AGTGCACTTC CTTGAGAGGA 1260

GGGAATGACC TCATTCTCTG TCCAGAATGT GGACTCCCTC TTCCTGAGCA TCTTATGGAA 1320

ATTACCCCAC CTTTGACTTG AAGAAACCTT CATCTAAAGC AAGTCACTGT GCCATCTTCC 1380

TGACCACTAC CCTCTTTCCT AGGGCATAGT CCATCCCGCT AGTCCATCCC GCTAGCCCCA 1440

CTCCAGGGAC TCAGACCCAT CTCCAACCAT GAGCAATGCC ATCTGGTTCC CAGGCAAAGA 1500

CACCCTTAGC TCACCTTTAA TAGACCCCAT AACCCACTAT GCCTTCCTGT CCTTTCTACT 1560

CAATGGTCCC CACTCCAAGA TGAGTTGACA CAACCCCTTC CCCCAATTTT TGTGGATCTC 1620

CAGAGAGGCC CTTCTTTGGA TTCACCAAAG TTTAGATCAC TGCTGCCCAA AATAGAGGCT 1680

TACCTACCCC CCTCTTTGTT GTGAGCCCCT GTCCTTCTTA GTTGTCCAGG TGAACTACTA 1740

AAGCTCTCTT TGCATACCTT CATCCATTTT TTGTCCTTCT CTGCCTTTCT CTATGCCCTT 1800

AAGGGGTGAC TTGCCTGAGC TCTATCACCT GAGCTCCCCT GCCCTCTGGC TTCCTGCTGA 1860

GGTCAGGGCA TTTCTTATCC CTGTTCCCTC TCTGTCTAGG TGTCATGGTT CTGTGTAACT 1920

GTGGCTATTC TGTGTCCCTA CACTACCTGG CTACCCCCTT CCATGGCCCC AGCTCTGCCT 1980

ACATTCTGAT TTTTTTTTTT TTTTTTTTTT TGAAAAGTTA AAAATTCCTT AATTTTTTAT 2040

TCCTGGTACC ACTACCACAA TTTACAGGGC AATATACCTG ATGTAATGAA AAGAAAAAGA 2100

AAAAGACAAA GCTACAACAG ATAAAAGACC TCAGGAATGT ACATCTAATT GACACTACAT 2160

TGCATTAATC AATAGCTGCA CTTTTTGCAA ACTGTGGCTA TGACAGTCCT GAACAAGAAG 2220

GGTTTCCTGT TTAAGCTGCA GTAACTTTTC TGACTATGGA TCATCGTTCC TT 2272

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 401 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Pro Gly Gly Pro Glu Pro Lys Pro Gly His Pro Pro Gln Thr Arg Gln
1 5 10 15

Ala Thr Ala Arg Thr Val Thr Pro Lys Gly Gln Leu Pro Gly Gly Lys
20 25 30

Ala Pro Pro Lys Ala Gly Ser Val Pro Ser Ser Phe Leu Leu Lys Lys
35 40 45

Ala Arg Glu Pro Gly Pro Pro Arg Glu Pro Lys Glu Pro Phe Arg Pro
50 55 60

Pro Pro Ile Thr Pro His Glu Tyr Met Leu Ser Leu Tyr Arg Thr Leu
65 70 75 80

Ser Asp Ala Asp Arg Lys Gly Gly Asn Ser Ser Val Lys Leu Glu Ala
85 90 95

Gly Leu Ala Asn Thr Ile Thr Ser Phe Ile Asp Lys Gly Gln Asp Asp
100 105 110

Arg Gly Pro Val Val Arg Lys Gln Arg Tyr Val Phe Asp Ile Ser Ala
115 120 125

Leu Glu Lys Asp Gly Leu Leu Gly Ala Glu Leu Arg Ile Leu Arg Lys
130 135 140

Lys Pro Ser Asp Thr Ala Lys Pro Ala Ala Pro Gly Gly Gly Arg Ala
145 150 155 160

Ala Gln Leu Lys Leu Ser Ser Cys Pro Ser Gly Arg Gln Pro Ala Ser
165 170 175

Leu Leu Asp Val Arg Ser Val Pro Gly Leu Asp Gly Ser Gly Trp Glu
180 185 190

Val Phe Asp Ile Trp Lys Leu Phe Arg Asn Phe Lys Asn Ser Ala Gln
195 200 205

Leu Cys Leu Glu Leu Glu Ala Trp Glu Arg Gly Arg Ala Val Asp Leu
210 215 220

Arg Gly Leu Gly Phe Asp Arg Ala Ala Arg Gln Val His Glu Lys Ala
225 230 235 240

Leu Phe Leu Val Phe Gly Arg Thr Lys Lys Arg Asp Leu Phe Phe Asn
245 250 255

Glu Ile Lys Ala Arg Ser Gly Gln Asp Asp Lys Thr Val Tyr Glu Tyr
260 265 270

Leu Phe Ser Gln Arg Arg Lys Arg Arg Ala Pro Leu Ala Thr Arg Gln
275 280 285

Gly Lys Arg Pro Ser Lys Asn Leu Lys Ala Arg Cys Ser Arg Lys Ala
290 295 300

Leu His Val Asn Phe Lys Asp Met Gly Trp Asp Asp Trp Ile Ile Ala
305 310 315 320

Pro Leu Glu Tyr Glu Ala Phe His Cys Glu Gly Leu Cys Glu Phe Pro
325 330 335

Leu Arg Ser His Leu Glu Pro Thr Asn His Ala Val Ile Gln Thr Leu
340 345 350

Met Asn Ser Met Asp Pro Glu Ser Thr Pro Pro Thr Cys Cys Val Pro
355 360 365

Thr Arg Leu Ser Pro Ile Ser Ile Leu Phe Ile Asp Ser Ala Asn Asn
370 375 380

Val Val Tyr Lys Gln Tyr Glu Asp Met Val Val Glu Ser Cys Gly Cys
385 390 395 400

Arg

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 352 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Thr Ser Ser Leu Leu Leu Ala Phe Leu Leu Leu Ala Pro Thr Thr
1 5 10 15

Val Ala Thr Pro Arg Ala Gly Gly Gln Cys Pro Ala Cys Gly Gly Pro
20 25 30

Thr Leu Glu Leu Glu Ser Gln Arg Glu Leu Leu Leu Asp Leu Ala Lys
35 40 45

Arg Ser Ile Leu Asp Lys Leu His Leu Thr Gln Arg Pro Thr Leu Asn
50 55 60

Arg Pro Val Ser Arg Ala Ala Leu Arg Thr Ala Leu Gln His Leu His
65 70 75 80

Gly Val Pro Gln Gly Ala Leu Leu Glu Asp Asn Arg Glu Gln Glu Cys
85 90 95

Glu Ile Ile Ser Phe Ala Glu Thr Gly Leu Ser Thr Ile Asn Gln Thr
100 105 110

Arg Leu Asp Phe His Phe Ser Ser Asp Arg Thr Ala Gly Asp Arg Glu
115 120 125

Val Gln Gln Ala Ser Leu Met Phe Phe Val Gln Leu Pro Ser Asn Thr
130 135 140

Thr Trp Thr Leu Lys Val Arg Val Leu Val Leu Gly Pro His Asn Thr
145 150 155 160

Asn Leu Thr Leu Ala Thr Gln Tyr Leu Leu Glu Val Asp Ala Ser Gly
165 170 175

Trp His Gln Leu Pro Leu Gly Pro Glu Ala Gln Ala Ala Cys Ser Gln
180 185 190

Gly His Leu Thr Leu Glu Leu Val Leu Glu Gly Gln Val Ala Gln Ser
195 200 205

Ser Val Ile Leu Gly Gly Ala Ala His Arg Pro Phe Val Ala Ala Arg
210 215 220

Val Arg Val Gly Gly Lys His Gln Ile His Arg Arg Gly Ile Asp Cys
225 230 235 240

Gln Gly Gly Ser Arg Met Cys Cys Arg Gln Glu Phe Phe Val Asp Phe
245 250 255

Arg Glu Ile Gly Trp His Asp Trp Ile Ile Gln Pro Glu Gly Tyr Ala
260 265 270

Met Asn Phe Cys Ile Gly Gln Cys Pro Leu His Ile Ala Gly Met Pro
275 280 285

Gly Ile Ala Ala Ser Phe His Thr Ala Val Leu Asn Leu Leu Lys Ala
290 295 300

Asn Thr Ala Ala Gly Thr Thr Gly Gly Gly Ser Cys Cys Val Pro Thr
305 310 315 320

Ala Arg Arg Pro Leu Ser Leu Leu Tyr Tyr Asp Arg Asp Ser Asn Ile
325 330 335

Val Lys Thr Asp Ile Pro Asp Met Val Val Glu Ala Cys Gly Cys Ser
340 345 350

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 265 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA from mRNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CATCCAGCCT GAGGGCTACG CCATGAACTT CTGCATAGGG CAGTGCCCAC TACACATAGC 60

AGGCATGCCT GGTATTGCTG CCTCCTTTCA CACTGCAGTG CTCAATCTTC TCAAGGCCAA 120

CACAGCTGCA GGCACCACTG GAGGGGGCTC ATGCTGTGTA CCCACGGCCC GGCGCCCCCT 180

GTCTCTGCTC TATTATGACA GGGACAGCAA CATTGTCAAG ACTGACATAC CTGACATGGT 240

AGTAGAGGCC TGTGGGTGCA GTTAG 265

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 139 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA from mRNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

CATCGCACCC CTTGAGTACG AGGCTTTCCA CTGCGAGGGG CTGTGCGAGT TCCCATTGCG 60

CTCCCACCTG GAGCCCACGA ATCATGCAGT CATCCAGACC CTGATGAACT CCATGGACCC 120

CGAGTCCACA CCACCCACC 139

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

ATGAACTCCA TGGACCCCGA GTCCACA 27

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

CTTCTCAAGG CCAACACAGC TGCAGGCACC 30

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Met Asn Ser Met Asp Pro Glu Ser Thr
1 5

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Leu Leu Lys Ala Asn Thr Ala Ala Gly Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

AGAATTCGCA TGCCATGGTC GACGAAGCTT TTTTTTTTTT TTTTTT 46

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

AGAATTCGCA TGCCATGGTC GACG 24

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GGCTACGCCA TGAACTTCTG CATA 24

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

ACATAGCAGG CATGCCTGGT ATTG 24

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

CTTGAGTACG AGGCTTTCCA CTG 23

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

ATTCGCATGC CATGGTCGAC GAAG 24

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GGAGCCCACG AATCATGCAG TCA 23

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

ACAGCAGGTG GGTGGTGTGG ACT 23

(2) INFORMATION FOR SEQ ID NO:19:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

CCAGCAGCCC ATCCTTCTCC 20

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

TCCAGGGCAC TAATGTCAAA CACG 24

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

ACTAATGTCA AACACGTACC TCTG 24

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 102 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Cys Ser Arg Lys Ala Leu His Val Asn Phe Lys Asp Met Gly Trp Asp
1 5 10 15

Asp Trp Ile Ile Ala Pro Leu Glu Tyr Glu Ala Phe His Cys Glu Gly
20 25 30

Leu Cys Glu Phe Pro Leu Arg Ser His Leu Glu Pro Thr Asn His Ala
35 40 45

Val Ile Gln Thr Leu Met Asn Ser Met Asp Pro Glu Ser Thr Pro Pro
50 55 60

Thr Cys Cys Val Pro Thr Arg Leu Ser Pro Ile Ser Ile Leu Phe Ile
65 70 75 80

Asp Ser Ala Asn Asn Val Val Tyr Lys Gln Tyr Glu Asp Met Val Val
85 90 95

Glu Ser Cys Gly Cys Arg
100

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 101 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Cys Lys Arg His Pro Leu Tyr Val Asp Phe Ser Asp Val Gly Trp Asn
1 5 10 15

Asp Trp Ile Val Ala Pro Pro Gly Tyr His Ala Phe Tyr Cys His Gly
20 25 30

Glu Cys Pro Phe Pro Leu Ala Asp His Leu Asn Ser Thr Asn His Ala
35 40 45

Ile Val Gln Thr Leu Val Asn Ser Val Asn Ser Lys Ile Pro Lys Ala
50 55 60

Cys Cys Val Pro Thr Glu Leu Ser Ala Ile Ser Met Leu Tyr Leu Asp
65 70 75 80

Glu Asn Glu Lys Val Val Leu Lys Asn Tyr Gln Asp Met Val Val Glu
85 90 95

Gly Cys Gly Cys Arg
100

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 101 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Cys Arg Arg His Ser Leu Tyr Val Asp Phe Ser Asp Val Gly Trp Asn

1 5 10 15

Asp Trp Ile Val Ala Pro Pro Gly Tyr Gln Ala Phe Tyr Cys His Gly
20 25 30

Asp Cys Pro Phe Pro Leu Ala Asp His Leu Asn Ser Thr Asn His Ala
35 40 45

Ile Val Gln Thr Leu Val Asn Ser Val Asn Ser Ser Ile Pro Lys Ala
50 55 60

Cys Cys Val Pro Thr Glu Leu Ser Ala Ile Ser Met Leu Tyr Leu Asp
65 70 75 80

Glu Tyr Asp Lys Val Val Leu Lys Asn Tyr Gln Glu Met Val Val Glu
85 90 95

Gly Cys Gly Cys Arg
100

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 102 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Cys Lys Lys His Glu Leu Tyr Val Ser Phe Arg Asp Leu Gly Trp Gln
1 5 10 15

Asp Trp Ile Ile Ala Pro Glu Gly Tyr Ala Ala Phe Tyr Cys Asp Gly
20 25 30

Glu Cys Ser Phe Pro Leu Asn Ala His Met Asn Ala Thr Asn His Ala
35 40 45

Ile Val Gln Thr Leu Val His Leu Met Phe Pro Asp His Val Pro Lys
50 55 60

Pro Cys Cys Ala Pro Thr Lys Leu Asn Ala Ile Ser Val Leu Tyr Phe
65 70 75 80

Asp Asp Ser Ser Asn Val Ile Leu Lys Lys Tyr Arg Asn Met Val Val
85 90 95

Arg Ser Cys Gly Cys His
100

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 102 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Cys Arg Lys His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Gln
1 5 10 15

Asp Trp Ile Ile Ala Pro Lys Gly Tyr Ala Ala Asn Tyr Cys Asp Gly
20 25 30

Glu Cys Ser Phe Pro Leu Asn Ala His Met Asn Ala Thr Asn His Ala
35 40 45

Ile Val Gln Thr Leu Val His Leu Met Asn Pro Glu Tyr Val Pro Lys
50 55 60

Pro Cys Cys Ala Pro Thr Lys Leu Asn Ala Ile Ser Val Leu Tyr Phe
65 70 75 80

Asp Asp Asn Ser Asn Val Ile Leu Lys Lys Tyr Arg Asn Met Val Val
85 90 95

Arg Ala Cys Gly Cys His
100

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 102 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
Cys Lys Lys His Glu Leu Tyr Val Ser Phe Arg Asp Leu Gly Trp Gln
1               5                  10                  15

Asp Trp Ile Ile Ala Pro Glu Gly Tyr Ala Ala Tyr Tyr Cys Glu Gly
            20                  25                  30

Glu Cys Ala Phe Pro Leu Asn Ser Tyr Met Asn Ala Thr Asn His Ala
        35                  40                  45

Ile Val Gln Thr Leu Val His Phe Ile Asn Pro Glu Thr Val Pro Lys
    50                  55                  60

Pro Cys Cys Ala Pro Thr Gln Leu Asn Ala Ile Ser Val Leu Tyr Phe
65                  70                  75                  80

Asp Asp Ser Ser Asn Val Ile Leu Lys Lys Tyr Arg Asn Met Val Val
                85                  90                  95

Arg Ala Cys Gly Cys His
            100
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 106 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Cys Cys Arg Gln Glu Phe Phe Val Asp Phe Arg Glu Ile Gly Trp His
1               5                  10                  15

Asp Trp Ile Ile Gln Pro Glu Gly Tyr Ala Met Asn Phe Cys Ile Gly
            20                  25                  30

Gln Cys Pro Leu His Ile Ala Gly Met Pro Gly Ile Ala Ala Ser Phe
        35                  40                  45
```

His Thr Ala Val Leu Asn Leu Leu Lys Ala Asn Thr Ala Ala Gly Thr
50 55 60

Thr Gly Gly Gly Ser Cys Cys Val Pro Thr Ala Arg Arg Pro Leu Ser
65 70 75 80

Leu Leu Tyr Tyr Asp Arg Asp Ser Asn Ile Val Lys Thr Asp Ile Pro
85 90 95

Asp Met Val Val Glu Ala Cys Gly Cys Ser
100 105

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 106 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Cys Cys Lys Lys Gln Phe Phe Val Ser Phe Lys Asp Ile Gly Trp Asn
1 5 10 15

Asp Trp Ile Ile Ala Pro Ser Gly Tyr His Ala Asn Tyr Cys Glu Gly
20 25 30

Glu Cys Pro Ser His Ile Ala Gly Thr Ser Gly Ser Ser Leu Ser Phe
35 40 45

His Ser Thr Val Ile Asn His Tyr Arg Met Arg Gly His Ser Pro Phe
50 55 60

Ala Asn Leu Lys Ser Cys Cys Val Pro Thr Lys Leu Arg Pro Met Ser
65 70 75 80

Met Leu Tyr Tyr Asp Asp Gly Gln Asn Ile Ile Lys Lys Asp Ile Gln
85 90 95

Asn Met Ile Val Glu Glu Cys Gly Cys Ser
100 105

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 105 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
Cys Cys Arg Gln Gln Phe Phe Ile Asp Phe Arg Leu Ile Gly Trp Asn
1               5                  10                  15

Asp Trp Ile Ile Ala Pro Thr Gly Tyr Tyr Gly Asn Tyr Cys Glu Gly
            20                  25                  30

Ser Cys Pro Ala Tyr Leu Ala Gly Val Pro Gly Ser Ala Ser Ser Phe
        35                  40                  45

His Thr Ala Val Val Asn Gln Tyr Arg Met Arg Gly Leu Asn Pro Gly
    50                  55                  60

Thr Val Asn Ser Cys Cys Ile Pro Thr Lys Leu Ser Thr Met Ser Met
65                  70                  75                  80

Leu Tyr Phe Asp Asp Glu Tyr Asn Ile Val Lys Arg Asp Val Pro Asn
                85                  90                  95

Met Ile Val Glu Glu Cys Gly Cys Ala
            100                 105
```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 105 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
Cys His Arg Val Ala Leu Asn Ile Ser Phe Gln Glu Leu Gly Trp Glu
1               5                  10                  15
```

Arg Trp Ile Val Tyr Pro Pro Ser Phe Ile Phe His Tyr Cys His Gly
20 25 30

Gly Cys Gly Leu His Ile Pro Pro Asn Leu Ser Leu Pro Val Pro Gly
35 40 45

Ala Pro Pro Thr Pro Ala Gln Pro Tyr Ser Leu Leu Pro Gly Ala Gln
50 55 60

Pro Cys Cys Ala Ala Leu Pro Gly Thr Met Arg Pro Leu His Val Arg
65 70 75 80

Thr Thr Ser Asp Gly Gly Tyr Ser Phe Lys Tyr Glu Thr Val Pro Asn
85 90 95

Leu Leu Thr Gln His Cys Ala Cys Ile
100 105

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

ATGAATTCCC ATGGACCTGG GCTGGMAKGA MTGGAT 36

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

ACGTGGGGTG GAATGACTGG AT 22

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

ATATTGGCTG GAGTGAATGG AT 22

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

ATGTGGGCTG GAATGACTGG AT 22

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

ACCTGGGCTG GCAGGACTGG AT 22

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

AGGACCTCGG CTGGAAGTGG AT 22

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

GGGATCTAGG GTGGAAATGG AT 22

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

AGGATCTGGG CTGGAAGTGG GT 22

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

AGCTGGGCTG GGAACGGTGG AT 22

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

ACATCGGCTG GAATGACTGG AT 22

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

TCATCGGCTG GAACGACTGG AT 22

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

ATGAATTCGA GCTGCGTSGG SRCACAGCA 29

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GAGTTCTGTC GGGACACAGC A 21

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CATCTTTTCT GGTACACAGC A 21

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CAGTTCAGTG GGCACACAAC A 21

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

GAGCTGCGTG GGCGCACAGC A 21

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

CAGCGCCTGC GGCACGCAGC A 21

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

TAAATCTTGG GACACGCAGC A 21

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CAGGTCCTGG GGCACGCAGC A 21

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

CCCTGGGAGA GCAGCACAGC A 21

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

CAGCTTGGTG GGCACACAGC A 21

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

CAGCTTGGTG GGAATGCAGC A 21